Is Renal Thrombotic Angiopathy an Emerging Problem in the Treatment of Ovarian Cancer Recurrences?

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Describe the need for additional vigilance regarding renal dysfunction when platinum, pegylated liposomal doxorubicin, bevacizumab, and gemcitabine are used for prolonged treatment of recurrent ovarian cancer in combination or sequentially following pre-existing renal damage.
2. Describe and quantify the risk of chronic kidney disease in patients treated for ovarian cancer.

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ABSTRACT

Background and Objective. Ovarian cancer is usually diagnosed at an advanced stage, with most patients undergoing surgery followed by platinum- and taxane-based chemotherapy. After initial clinical remission, the majority recur, leading to additional treatments, including not only platinum and taxanes but also pegylated liposomal doxorubicin (PLD), gemcitabine, topotecan, and, more recently, bevacizumab, which may extend survival times. PLD, in particular, has been extensively studied by our group, with encouraging therapeutic results. We, however, observed

instances of chronic kidney disease (CKD) developing among patients who received long-term treatment for recurrent ovarian cancer. To document the frequency and contributing factors to the emergence of CKD, we initiated a retrospective review at two institutions.

Patients and Methods. Fifty-six consecutive patients with recurrent ovarian cancer receiving treatment at New York University Cancer Institute were reviewed for the presence of renal disease in 1997–2010. At Shaare Zedek Medical Center, 73 consecutive patients with ovarian cancer were

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reviewed in 2002–2010. Patients were diagnosed with CKD if they had an estimated GFR <60 mL/minute per 1.73 m^2 for >3 months and were staged according to the National Kidney Foundation guidelines.

Results. Thirteen patients (23%) developed stage ≥ 3

CKD. Three patients had renal biopsies performed that showed thrombotic microangiopathy.

Conclusions. CKD is emerging as a potential long-term consequence of current chemotherapy for recurrent ovarian cancer. *The Oncologist* 2012;17:1534–1540

INTRODUCTION

Ovarian cancer is the second most common gynecological cancer and the fifth most frequent cause of cancer death in women. The majority of patients present in stage III, requiring surgery for diagnosis, tumor debulking, and staging followed by either i.v. carboplatin or intraperitoneal (i.p.) cisplatin (in the absence of gross residual disease) and paclitaxel. Despite high response rates to first-line treatment, $\sim 80\%$ of patients experience disease recurrence with a 5-year overall survival rate of 25%–50%. Treatment for clinical recurrences beyond 6 months commonly involves the previously mentioned drugs. Pegylated liposomal doxorubicin (PLD), gemcitabine, topotecan, and, more recently, bevacizumab also play important roles in early recurrence or later in combination with platinum [1]. The choice of second-line treatment is driven by the side-effect profile of the drug regimens and their impact on patients' quality of life. Prolonged control of disease from these sequential treatments has given rise to labeling ovarian cancer as a "chronic disease," with a heightened awareness of treatment-related morbidity. In fact, a preliminary analysis of our experience with PLD, a drug that was partly developed within our institutional trials, identified a high incidence of chronic kidney disease (CKD) and hypertension among women undergoing long-term treatments for recurrence [2].

METHODS

PLD has been used by our group since we performed and published the original phase I study in 1995 [3]. We then incorporated PLD into a number of additional treatment studies in ovarian cancer patients. Our current clinical trial of PLD and bevacizumab for recurrent ovarian cancer at New York University (NYU) (ClinicalTrials.gov identifier, NCT00846612) increased our awareness of the development of CKD and hypertension during long-term treatment. This prompted a retrospective analysis of patients at two institutions (NYU Cancer Institute and Shaare Zedek Medical Center [SZMC]) where, in sequential studies, PLD was often continued beyond six cycles as maintenance [4, 5]. NYU Institutional Review Board approval was obtained for a review of our cases involving patients who received PLD. Additionally, cases of patients who received both PLD and bevacizumab had a separate approval as a prospective clinical trial in the same population (ClinicalTrials.gov identifier, NCT00945139; manuscript to be published in *Annals of Oncology*). Fifty-six consecutive patients at NYU with recurrent ovarian cancer in 1997–2010 treated with PLD for at least six cycles and followed for >1 year were reviewed for the presence of renal disease [2]. Excluded were patients with pre-existing stage ≥ 3 CKD and/or hydronephrosis. At SZMC, a similar retrospective review was performed

for patients treated with PLD in 2002–2010, focusing on patients who developed stage 4 or 5 CKD.

For each patient, demographic information, laboratory data, and clinical outcomes were collected, including blood pressure and serum creatinine as markers of renal function. The glomerular filtration rate (GFR) was estimated in mL/minute per 1.73 m^2 for each measured serum creatinine using the Modification of Diet in Renal Disease study equation [6]. Patients were diagnosed with CKD if they had either kidney damage or an estimated GFR (eGFR) <60 mL/minute per 1.73 m^2 for >3 months and were staged by eGFR in mL/minute per 1.73 m^2 according to the National Kidney Foundation guidelines [7]. Kidney damage was defined by pathologic abnormalities or markers of damage, including abnormalities on blood and urine tests and radiologic studies. Specifically, patients with stage 3 CKD had a moderate decrease in eGFR of 30–59 mL/minute per 1.73 m^2 , patients with stage 4 CKD had a severe decrease in eGFR of 15–29 mL/minute per 1.73 m^2 , and patients with stage 5 CKD had kidney failure with an eGFR <15 mL/minute per 1.73 m^2 . Patients were classified as hypertensive if their systolic blood pressure was >140 mmHg and diastolic blood pressure was >90 mmHg on at least three measurements over three separate clinic appointments [8]. Three of the patients manifesting rapid progression beyond stage 3 CKD were subject to renal biopsies at three different institutions (see below).

RESULTS

For treated patients at NYU, the median age at diagnosis of ovarian cancer was 56 years (range, 31–83 years), of these 86% (48 of 56) presented with stage III or stage IV disease. All patients received PLD, either by itself or in various doublets with other anticancer drugs when enrolled in clinical trials. PLD was often continued beyond six cycles in the absence of disease progression or prohibited toxicities (adherence to the black box U.S. Food and Drug Administration warning on cumulative dosing seemed unnecessary based on our prior published experience) [9, 10]. The median number of chemotherapy regimens was four (range, 2–10), with a median follow-up time of 50 months (range, 10–147 months). The median cumulative dose of PLD received was 470 mg/m^2 (range, 80–3,600 mg/m^2). The median total time of treatment was 47 months (range, 6–140 months), with a median time of treatment since recurrence of 30 months (range, 3–125 months). The overall survival percentage at closure of data analysis was 53.6% (30 of 56).

No patients manifested congestive heart failure. Hypertension—often accompanied by moderate proteinuria—was a common finding and frequently the first sign of CKD. Table 1 shows the treatment regimens that were given for disease re-

Table 1. Treatment regimens for disease recurrence and other features in patients manifesting stage 3–5 CKD

Patient	Age at cancer diagnosis/CKD diagnosis (yrs)	Drugs for recurrence prior to development of CKD	Cumulative dose of PLD (mg/m ²)	Time on PLD to development of stage 3 CKD (mos)	Stage of HTN achieved	Comments and follow-up
Stage 3 CKD (eGFR ^a 30–59 mL/minute per 1.73 m ²)						
1^c	63/67	<i>To + O → T, C + PLD → PLD, B, G</i>	460	6.8	1	Had evidence of hemolysis on G; currently stable clinically after a vaccine study and letrozole
2^d	58/63	<i>C + PLD → O + PLD</i>	840	9.7	1	Unilateral hydronephrosis; last known with cancer progression in 2009 (age 64 yrs)
3 ^e	53/58	C + PLD → PLD, G	1,240	39.0	1	Had evidence of hemolysis and thrombocytopenia on G; died with progression at age 58 yrs
4^e	68/69	<i>C + PLD → PLD</i>	2,116	3.8	1^b	Slowly rising creatinine; no treatment for 2+ yrs after resection of squamous cell carcinoma of tongue
5 ^c	58/63	C + PLD → PLD, B	2,200	25.5	No HTN	Small bowel obstruction resolved with ileostomy and G; dead as a result of disease at age 65 yrs
Stage 4 CKD (eGFR 15–29 mL/minute per 1.73 m ²)						
6^c	61/65	<i>C + G + placebo, O + PLD → PLD + B</i>	510	6.8	1	Dead as a result of disease at age 66 yrs
7 ^c	63/66	C, <i>To + O, PLD + B</i>	1,010	4.7	2 ^b	Dead as a result of disease at age 67 yrs with rising creatinine
8^c	48/55	<i>To, C, PLD, PLD + B</i>	2,000	66.0	2	Rising creatinine disqualified her for other treatments; dead as a result of disease at age 56 yrs
Stage 5 CKD (eGFR <15 mL/minute per 1.73 m ²)						
9 ^c (patient 3)	58/61	C, PLD, G	880	24.0	2	On T, To, and later etoposide for disease progression with stable creatinine for 2+ yrs
10^c (patient 1)	64/65	<i>C, PLD + B, G</i>	905	3.0	2	Dead as a result of disease at age 71 yrs
11 ^c	60/63	C, PLD, B	960	22.4	2	Dead as a result of disease at age 64 yrs
12 ^d	58/64	C + PLD → PLD	1,120	11.3	2 ^b	No treatment for 2+ yrs after rising creatinine; died as a result of congestive heart failure and end-stage renal disease at age 66 yrs (no evidence of disease)
13^e	58/61	<i>C + PLD → PLD</i>	1,730	32.1	2	Hemodialysis for 2 years; dead as a result of disease at age 67 yrs

All patients received carboplatin and paclitaxel induction. Bold font indicates those who received i.v. (patient 13) or intraperitoneal cisplatin during induction or as consolidation.

Treatment protocols are shown in italics: To + O, PLD + B, OCEANS (C + G +/- B) [23].

^aGFR estimated using the four-variable Modification of Diet in Renal Disease equation.

^bPatients with pre-existing hypertension.

^cMutation negative.

^dBRCA2 mutation.

^eBRCA1 mutation.

Abbreviations: B, bevacizumab; C, carboplatin; CKD, chronic kidney disease; G, gemcitabine; GFR, glomerular filtration rate; HTN, hypertension; O, oxaliplatin; PLD, pegylated liposomal doxorubicin; T, paclitaxel; To, topotecan.

Figure 1. Core needle biopsy of kidney (patient 1 at New York University). **(A):** Subsegmental mesangiolysis of the glomerulus with swollen endothelial cells. Fragmented RBCs (arrow) and fibrin are present in the capillary lumen. Silver stain, 40 $\times$ magnification. **(B):** Segmental solidification of the glomerular tuft with hilar material, mesangiolysis, and the development of a balloon-like structure (arrow) from expansion of the subendothelium and subsegmental loss of the mesangial tree. Periodic acid-Schiff stain, 40 $\times$ magnification. **(C):** Electron micrograph showing trapped and fragmented RBCs (arrow) within severely widened subendothelial space and mesangiolysis with remnants of cellular debris.

currence, with clinical protocols identified in *italics*. During initial induction therapy after diagnosis, the patients all received platinum-based therapy (usually carboplatin, but occasionally oxaliplatin). Carboplatin plus PLD followed by PLD maintenance was a common regimen used, and oxaliplatin plus topotecan was also under study. Seven patients had received cisplatin, six of them via the i.p. route during consolidation (bold font in Table 1). Bevacizumab was also given to several patients as part of our prospective clinical trial involving PLD and bevacizumab. Overall, 13 patients (23%) developed stage ≥ 3 CKD during treatment for disease recurrence (Table 1). Of these 13 patients, two had pre-existing renal dysfunction that was stage < 3 CKD at the outset. During treatment, one progressed to stage 4 CKD and another progressed to stage 5 CKD. Three of these patients also had pre-existing hypertension that worsened during therapy. The two above patients with pre-existing renal disease and two others (total of four of 56) had stage 1 or stage 2 CKD when recurrence was diagnosed.

We further analyzed the patients who developed stage 5 CKD. Two of the patients at NYU underwent renal biopsies that showed thrombotic microangiopathy (patient 1 and patient 3, see below). One underwent hemodialysis with improvement in renal function and one refused dialysis and eventually succumbed to CKD. For the remaining patients, gradual improvement in the GFR allowed holding off dialysis. Several went on to receive other cancer treatments in spite of frequent exclusions from clinical trials because of their poor renal function.

At SZMC, the charts of 73 consecutive patients receiving PLD for recurrent ovarian cancer as well as 56 consecutive patients receiving PLD for breast cancer or sarcoma in 2002–2010 were reviewed for the presence of stage 4 or 5 CKD. There were two patients in the ovarian cancer treatment group with stage 4 or 5 CKD, whereas none in the breast cancer and sarcoma group had CKD stage > 3 . Of the two patients, one developed stage 5 CKD with evidence of thrombotic microangiopathy (patient 2, see below) on renal biopsy. The other patient had stage 4 CKD following prolonged treatment with PLD, with partial recovery of renal function upon discontinu-

ation of PLD. Of note, this patient was further treated with weekly paclitaxel, during which her kidney function remained stable. However, as her disease progressed, a trial with two courses of carboplatin resulted in rapid deterioration of kidney function with a rise in creatinine from 1.8 to 3.1 mg/dL (equivalent to a decrease in eGFR from 30 mL/minute per 1.73 m² to 18 mL/minute per 1.73 m²), thus indicating that kidney function remains highly susceptible to relatively minimal toxic drug insults.

CASE REPORTS

The courses of three patients who underwent renal biopsies to further assess their stage 5 CKD are described.

Patient 1

This 71-year-old female patient had optimal surgical debulking of a stage III high-grade papillary serous epithelial ovarian cancer at the age of 64 years, followed by first-line therapy at NYU with carboplatin and paclitaxel followed by four cycles of i.p. cisplatin. She had normal baseline renal function with a serum creatinine level of 0.9 mg/dL, which increased to 1.3 mg/dL after the first dose of cisplatin. Her renal function remained stable enough for enrollment 6 months later in a phase II clinical trial of PLD plus bevacizumab for the treatment of refractory ovarian cancer upon disease progression [11]. PLD (total cumulative dose, 905 mg/m²) and bevacizumab were given from September 2008 until November 2009. During the clinical trial, her renal function slowly worsened to a creatinine level of 2.0 mg/dL with evidence of proteinuria. She also experienced headaches associated with hypertension, requiring treatment with a β -blocker.

Abdominal pain and a rising cancer antigen (CA)-125 level prompted resumption of treatment. When she started gemcitabine, her serum creatinine level was 2.5 mg/dL. A rise in creatinine to 5.0 mg/dL (eGFR, 10.0 mL/minute per 1.73 m²) coupled with dyspnea and worsening edema led to her hospitalization in June 2010. A renal biopsy showed diffusely acute and focally chronic thrombotic microangiopathy. There was

also tubular atrophy, interstitial fibrosis, and chronic inflammation (Fig. 1). The patient's symptoms gradually resolved and her creatinine level improved to 3.0 mg/dL, but intra-abdominal cancer progression eventually prompted treatment with paclitaxel and subsequently with carboplatin. In May 2011, her functional status declined acutely with the onset of seizures, encephalopathy, and lower extremity ischemia, with a clinical picture compatible with nonbacterial thrombotic endocarditis. She was hospitalized and died 1 week later.

Patient 2

This 39-year-old female patient was diagnosed at SZMC with ovarian cancer at the age of 34 years. She received first-line treatment with carboplatin and paclitaxel. Upon disease recurrence, she received PLD in September 2006 followed by long-term maintenance to a cumulative dose of 1,445 mg/m². At the start of PLD, her baseline renal function was normal, with a creatinine level of 0.7 mg/dL. PLD was discontinued in January 2010 upon noting an increased creatinine level. Before developing stage 5 CKD with a peak creatinine level of 5.5 mg/dL (eGFR, 9.4 mL/minute per 1.73 m²), she received two further doses of carboplatin in May 2010. During that time, she was symptomatic with hypertension, fluid retention, pleural effusion, and anemia. Renal biopsy showed thrombotic microangiopathy (Fig. 2). The patient was treated with corticosteroids and plasmapheresis, with transient improvement, and was then managed with hemodialysis for 5 months. There was partial recovery of kidney function, with a creatinine value of 2.7 mg/dL (eGFR, 21.4 mL/minute per 1.73 m²). With progression of her cancer, she resumed chemotherapy with weekly paclitaxel, but further progression with enlarging pelvic masses, rectal obstruction, and finally intestinal perforation led to her death in February 2011.

Patient 3

This 63-year-old female patient was diagnosed at Vanderbilt University Medical Center with poorly differentiated ovarian cancer at the age of 58 years. When seen at NYU for consultation in June 2005, she was undergoing her third series of treatments with carboplatin for repeated recurrences. She had received six cycles of carboplatin and paclitaxel as first-line treatment, and then carboplatin with gemcitabine. After progression and debulking surgery, she received six cycles of PLD. With a rising CA-125 level, PLD was then resumed in October 2007 to February 2009. The total cumulative dose of PLD was 880 mg/m². Despite a normal creatinine clearance at baseline (eGFR, 98.0 mL/minute per 1.73 m²), she experienced a gradual decline in renal function and developed stage 5 CKD (peak creatinine, 5.0 mg/dL; eGFR, 9.4 mL/minute per 1.73 m²) and hypertension. She had a renal biopsy at Vanderbilt that showed thrombotic microangiopathy, with findings similar to those of patient 1 and patient 2. She had slow improvement in renal function off PLD. At the time of writing, her creatinine level was 3.5 mg/dL and her eGFR was 13–16 mL/minute per 1.73 m². Paclitaxel, topotecan, and etoposide were given sequentially (at renal function–adjusted doses) for

cancer progression, and she fortunately has experienced some regression of disease with each regimen.

DISCUSSION

CKD is a potential long-term consequence of the current treatments for ovarian cancer. Platinum agents have been shown to cause renal tubular injury since the clinical phase I study of cisplatin in 1970. Cisplatin use is associated with dose-dependent nephrotoxicity and a consistent subclinical and often permanent reduction in GFR, only partially prevented by hydration and the avoidance of nephrotoxic antibiotics [12]. Presumably, tubular cells exposed to high concentrations of cisplatin and its chemically reactive aquated species undergo injury and death. Cisplatin may also cause injury to renal endothelium, resulting in decreased blood flow and ischemic injury, contributing to a decline in the GFR [13]. In comparison, carboplatin, a second-generation platinum approved in 1989, is much less nephrotoxic. Nevertheless, tubular proteinuria is consistently demonstrated following treatment [14]. Our experience—including the absence of renal toxicity resulting from PLD in patients with breast cancer, sarcoma, and other cancers—suggests that prior exposure to platinum agents may predispose to additional renal damage when women with recurrent ovarian cancer receive more platinum agents such as PLD, gemcitabine, and bevacizumab.

Since its introduction in the 1990s, PLD has emerged as one of the most commonly used agents for recurrent ovarian cancer [15]. This formulation of doxorubicin using liposomal encapsulation lessens its uptake by the cardiac muscle and drastically prolongs the half-life of the liposomal drug in the vascular compartment. The unique pharmacokinetic profile of PLD causes “passive” intratumor drug accumulation and attenuated systemic doxorubicin toxicities at the expense of higher incidences of skin and mucosal toxicities [5, 16].

We previously reported cardiac and overall safety data of PLD after prolonged administration with seemingly good control of disease [4, 10]. Of note, six of our patients with stage 3–5 CKD had *BRCA* mutations (Table 1). These mutation carriers seem to particularly benefit from treatment with platinum agents and other DNA damaging agents such as PLD [17]. The current experience, however, highlights the insidious development of renal dysfunction and hypertension in several patients on long-term therapy [2]. Among all our patients who developed CKD, PLD use is a common denominator—we had used PLD (frequently combined with carboplatin followed by PLD alone as maintenance) as first-line recurrence treatment for years. Consequently, our patients received maintenance treatment for a longer time than in other series.

Doxorubicin is a well-known inducer of nephropathy in rat and murine models, but it has been proven to be safe in its wide clinical use for the treatment of breast cancer, uterine cancer, sarcomas, and hematologic malignancies, including multiple myeloma—a disease that is often complicated by CKD. The histopathology of doxorubicin-treated rodent kidneys is characterized by injury to the podocytes followed by glomerulosclerosis, increased intracellular products of oxidative stress, mesangial expansion, and tubular dilatation [18, 19]. These

Figure 2. Core needle biopsy of kidney (patient 2 at Shaare Zedek Medical Center). (A): Fibrinoid necrosis (arrows) of the glomerular arteriole. Masson's trichrome stain, 630× magnification. (B): Marked expansion of subendothelial space creating a balloon-like structure (arrow). Jones' methenamine silver stain, 630× magnification. (C): Electron microscopy micrograph. RBCs (arrow) are accumulating in the expanded subendothelial space. In addition, diffuse effacement of foot processes of visceral epithelial cells (podocytes) is noted.

changes resemble those of human focal glomerulosclerosis [20]. Doxorubicin is also known to decrease urinary levels of nitric oxide, thereby promoting salt-sensitive hypertension in the rat model [21]. In rodents, the liposomal formulation is associated with attenuated cardiotoxicity and also with less nephrotoxicity, which is otherwise the cumulative dose-limiting toxicity of doxorubicin [22]. The attenuated cardiotoxicity afforded by PLD may conceivably result in nephrotoxicity during its protracted use, particularly when preceded or combined with other kidney insults.

More recently, bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), was added to agents used against recurrent ovarian cancer [23]. The production of VEGF by renal podocytes maintains the adjacent glomerular endothelium. Deletion of VEGF from renal podocytes in mice resulted in thrombotic glomerular injury. Clinically, glomerular disease characteristic of thrombotic microangiopathy has been described in humans after bevacizumab therapy [24]. The nucleoside analog gemcitabine has been associated with hemolytic uremic syndrome, characterized by hypertension, thrombocytopenia, renal failure, and microangiopathic hemolytic anemia [25]. Protracted use of platinum, PLD, and gemcitabine may lower the threshold for

or predispose to bevacizumab-induced renal thrombotic microangiopathy.

Treatments for recurrent ovarian cancer result in clinical benefit and prolongation of survival times. However, our findings suggest that platinum, PLD (in large cumulative doses), bevacizumab, and possibly gemcitabine may result in cumulative kidney damage. Awareness of these long-term complications should open the way for studies on treatment strategies designed to minimize renal complications.

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EDITOR'S NOTE: We publish in this issue a brief series of related papers and letters that examine possible side effects of long-term exposure to pegylated liposomal doxorubicin (PLD). See pages 1541–1546 for a report of squamous cell carcinoma (SCC) of the mouth in non-smoking women with recurrent ovarian cancer; and pages 1594–1599 for three Letters to the Editor that relate several cases of SCC of the oral cavity in patients with long-term PLD exposure.